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Chemical composition and physiological bioactivities of *Stiefia multicaulis* (Vahl) Soják Vahl grown in Palestine

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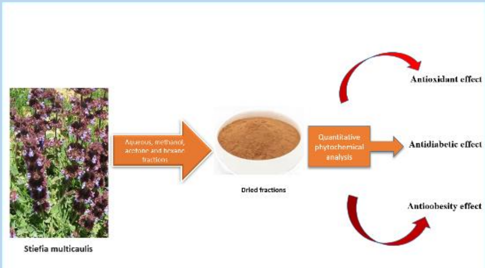
Abstract: **Background:** Herbal products encompass a wide range of natural substances that show great potential as therapeutic materials. Consequently, there has been a substantial investigation into the therapeutic potential of numerous plant species in recent times. The present study sought to determine the components and assess the antioxidant, antilipase, α-amylase, and α-glycosidase enzyme inhibitory activities of *Stiefia multicaulis* (Vahl) Soják Vahl hexane, acetone, methanol, and aqueous fractions. **Methods:** Standard pharmacopeia methods were used to conduct screenings for both quantitative and qualitative phytoconstituents. The lipase, α-amylase, and α-glycosidase enzyme inhibitory activities were assessed using established reference methods. In addition, the antioxidant activity was assessed using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. **Results:** The screening methods of pharmacopeias revealed that *S. multicaulis* contains a wide range of secondary metabolites, especially tannins. However, the most potent antioxidant, antilipase, α-glucosidase, and α-amylase inhibitory activities were acetone fraction, hexane, methanol, and aqueous *S. multicaulis* fractions, respectively. **Conclusion:** The current study outcomes are the first on the a-amylase, lioase, α-glucosidase inhibitory activities of S.multicaulis four splvent fractions. Further invesigations are needed to assess the invivo potential of these plant fractions in animal models.



Keywords: *Stiefia multicaulis*; Antioxidant; Antilipase; α-Glucosidase; α-Amylase.

Introduction

As a result of its usefulness in the prevention and treatment of various diseases, phytomedicine has emerged as a staple of contemporary medicine. Their use as both conventional and complementary therapies dates back to ancient civilizations. Also, most modern medications are derived from plants because of the wide range of systems they can affect in the human body. Natural medicines and their derivatives are widely believed to be safe, but research has shown that they can have serious side effects or even be fatal if used improperly [1-4].

Recently, oxidative stress has become a widespread phenomenon. Once we have a lot of free radicals that exceed antioxidants, they can fight our body by many diseases, such as atherosclerosis, diabetes, cancer, Parkinson's, and Alzheimer's. Many scientists recommend avoiding the production of free radicals by minimizing their sources, such as stopping smoking and avoiding radiation and pollution [4, 5].

However, there is no way to avoid oxidative stress, but many antioxidants can help us, such as vitamin E and vitamin C supplements and beta-carotene supplements. In addition, a daily diet containing a variety of fruits and vegetables is also considered one of the methods used to obtain enough antioxidants [6].

Around 30% of the world's population is overweight, making obesity a global health epidemic, according to WHO biostatistical evaluations. On top of that, obesity is a major health problem in and of itself, and it often leads to other problems, including diabetes, heart disease, and gastrointestinal issues. The function of hyperlipidemia in the development of obesity has been the subject of recent research. In this regard, regulating obesity may benefit from a reduction in dietary fat or its absorption through the inhibition of the lipase enzyme [7, 8].

People with diabetes mellitus (DM), a chronic, lifelong illness, experience hyperglycemia due to the body's incapacity to digest fat, carbs, and lipids. Over the last several decades, there has been a steady rise in the frequency of diabetes mellitus, with 422 million people worldwide living with the condition in 2014, up from 180 million in 1980. With 1.6 million deaths over the previous two years, it was the seventh most common cause of death, according to the World Health Organization [9-11].

Stiefia multicaulis (Vahl) Soják Vahl (family Lamiaceae) is an annual plant that reaches 30-50 cm. The leaves are long-petiolated, crenulate, ovate or oblong, obtuse, cordate or rounded at base, sometimes with two lateral minute segments; indumentum of mostly stellate dense appressed hairs which are denser still on the grayish lower face, while the floral leaves are sessile, membranous and oval. The calyx is 2-labiate, pale green or purple, glabrous with sessile glands, glandular-hairy or pilose. The origin is the west Irano-Turanian, extending into the Eastern regions of the Mediterranean basin. The major ingredients of *S. multicaulis* essential oil that are present in a high concentration are camphor, 1,8-cineole, borneol, and α-pinene [12]. While it is often used in traditional medicine to treat colds, sore throats, and stomachaches, it has also been studied for its antispasmodic and antiseptic qualities [13].

The present study was undetaken to determine the components and assess the antioxidant, antilipase, α-amylase, and α-glycosidase enzyme inhibitory activities of *Stiefia multicaulis* (Vahl) Soják Vahl hexane, acetone, methanol, and aqueous fractions.

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Material and methods

Instruments

Spectrophotometer (Jenway 7315, England), Rotavap (Heidolph OB2000-VV2000, Germany), stir-mixer (Tuttnauer, Jerusalem), balance (Rad wag, AS 220/c/2 in Poland), freeze dryer (Mill rock technology-BT85, China), weighing scale (Adam Equipments, USA).

Plant collection and preparation

S. multicaulis leaves were collected in July 2018 from Wadi-Qana area in Nablus/Palestine. The plant was characterized in the Herbal Products Laboratory at An-Najah National University and kept within the voucher specimen code Pharm-PCT-2123.

The *S. multicaulis* leaves were rinsed with purified water multiple times before being left to dry in the shade at room temperature. The drying process took approximately one month, after which they were crushed roughly and stored in a tightly sealed glass jar until needed again.

Fractionation method

The dried powdered leaves were fractionated by four types of solvents: methanol, acetone, hexane, and distilled water. The dried leaves were soaked in 1 liter of each solvent sequentially and each fraction was placed in a shaker device for about two days at room temperature. The filtrates were concentrated under a vacuum on a rotary evaporator or dried using a freeze drier. The final fractions were stored in a refrigerator [14].

Phytochemical analysis

Each fraction (methanol, acetone, hexane, and water) underwent qualitative chemical analysis for each primary and secondary metabolic compound such as steroids, terpenoids, starch, carbohydrates, cardiac glycosides, flavonoids, tannins, monosaccharide, protein, reducing sugar, alkaloids, phenols, and saponins. Phytochemical analysis was executed according to the standard qualitative analytical assays as described by Harborne and Evans [15, 16].

Quantitative total phenol content

Total phenol content was determined in the four plant fractions using the spectrophotometric and Folin-Ciocalteu's reagent. In milligrams of gallic acid, equivalent per gram of plant fractions is the concentration that was determined from the absorbance measurements [17].

Determination of total tannin content

Its total amount of tannin was ascertained using a modified Folin-Denis colorimetric technique. The calibration curve will be constructed by making serial dilutions from an aqueous stock solution of 1 mg/ml tannic acid. Catechin equivalent concentrations (mg CAE/g) for all plant components.

Porcine pancreatic lipase enzyme inhibitory method

By dissolving 100 mg of each plant fraction in 100 ml of 10% DMSO, a working solution (1 mg/ml) was prepared for each *S. multicaulis* fraction. Subsequently, the solution was diluted to reach various concentrations (0.05, 0.1, 0.2, 0.3, and 0.4 mg/ml). Be that how it may, the following equation was used to determine the lipase enzyme inhibitory potential (I%)[18]:

$$I\ (\%) = [ABS_{blank} - ABS_{test}]/[\ ABS_{blank}])\ ^{*}100\%$$

α-Amylase inhibitory method

To make a working solution (1 mg/ml) from each *S. multicaulis* plant fraction, 25 mg of each fraction was dissolved in a small quantity of 10% DMSO. To this, 25 ml of a buffer solution was added. Various dilutions (0.01, 0.05, 0.07, 0.1, and 0.5 mg/ml) were obtained using the buffer. The absorbance was measured at 540 nm using a UV-Vis Spectrophotometer, with Acarbose serving as a positive reference solution. The inhibition ability against α-amylase was determined using a specific equation.

$$I\ (\%) = [ABS_{blank} - ABS_{test}]/[\ ABS_{blank}])\ ^{*}100\%$$

Where I (%), is the α-amylase inhibitory percentage [19].

α-Glucosidase inhibitory activity

One milligram per milliliter of phosphate buffer was used to create a workable solution from 100 milligrams of each *S. multicaulis* leaf portion. Phosphate buffer diluted the solution to get different concentrations (100, 200, 300, 400, 500 μg/ml). The next calculation was used to assess the inhibiting action of α-glucosidase.

$$I\ (\%) = [ABS_{blank} - ABS_{test}]/[\ ABS_{blank}])\ ^{*}100\%$$

Where I (%), is the percentage inhibition of α-glucosidase [20] .

Free radical scavenging activity

A mixture containing 1 mg/ml of each S. multicaulis leaf fragment was made by dissolving 100 mg of each fraction in 100 ml of methanol. Subsequently, the solution was further diluted with methanol to achieve various concentrations ranging from 2 to 100 μg/ml. A UV-Vis spectrophotometer measured the absorbance at 517 nm, with Trolox functioning as a control. The results were contrasted with the control. The subsequent formula was used to compute the antioxidant activity.

$$I\ (\%) = [ABS_{blank} - ABS_{test}]/[\ ABS_{blank}])\ ^{*}100\%$$

where I (%), is the percentage of antioxidant activity [21, 22).

Statistical analysis

All tests were repeated three times, and the obtained results are shown as means ± SD.

Results and discussion

Phytochemical analysis

Table 1 shows the phytochemical identification test outcomes, which revealed that *S. multicaulis* all fractions containing tannins, while the acetone, hexane and methanol fractions contain glycosides. Moreover, the aqueous fraction was the only one containing phenols.

Table (1): The chemical analysis of *S. multicaulis* extracts.

Plant products	Acetone	Hexane	Methanol	Water
Protein	-	-	+	+
Carbohydrate	-	-	+	+
Tannin	+	+	+	+
Flavonoid	-	-	-	-
Saponin	-	-	-	-
Glycosides	+	+	+	-
Phenol	-	-	-	+

Total tannin content

Estimations of total tannin contents in *S. multicaulis* leave methanol, hexane, acetone and aqueous fractions were conducted according to standard analytical method. As well as catechin was used as a reference compound while the absorbance was measured at λmax =500 nm. However, from the standard calibration curve (Fig. 1), the total tannin content in all plant fractions was calculated according to the following formula:

$Y = 0.001X + 0.002$, $R^2 = 0.991$, Where

Y- Absorbance at 500 nm

X- Total tannin in the plant fraction.

The quantitative tannin contents of *S. multicaulis* leave methanol, hexane, acetone, and aqueous fractions are presented in Table 2 and showed that the aqueous fraction has the highest percent of tannin contents compared with other fractions.

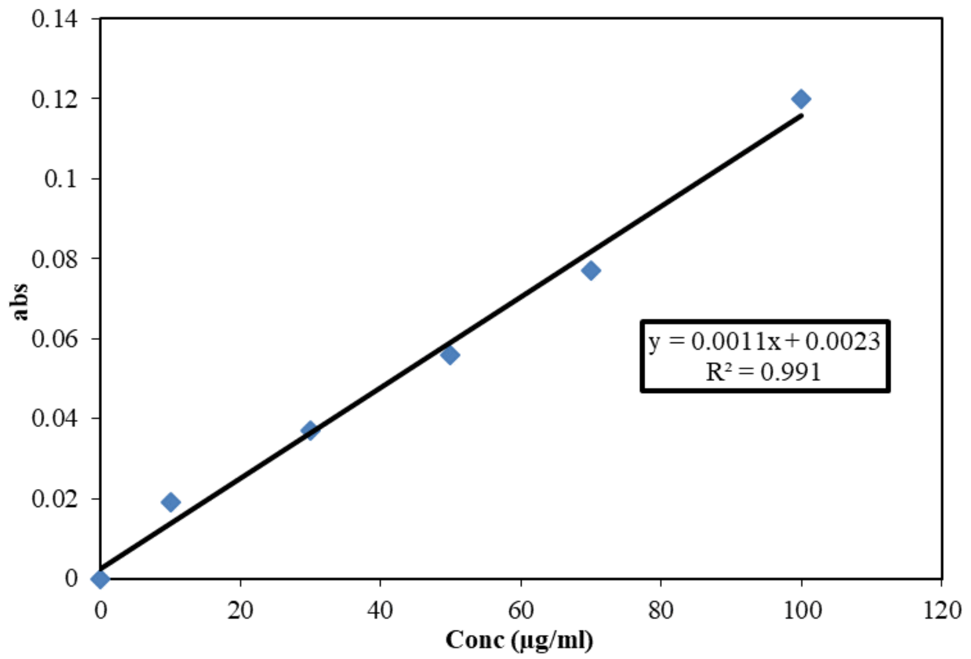

Figure (1): Standard calibration curve of Catechin.

Total phenol contents

Estimating total phenols in *S. multicaulis* leaves was conducted in the aqueous fraction, while the other fractions did not contain phenolic compounds. The total phenols were expressed as mg/g Gallic acid equivalent and the standard calibration curve of Gallic acid (Fig. 2) was constructed to estimate the total phenol content in the plant aqueous fraction using the following formula:

Y = 0.009X+ 0.021, R^2 =0.992, Where

Y- Absorbance at 760 nm

X- Total phenol in the aqueous fraction.

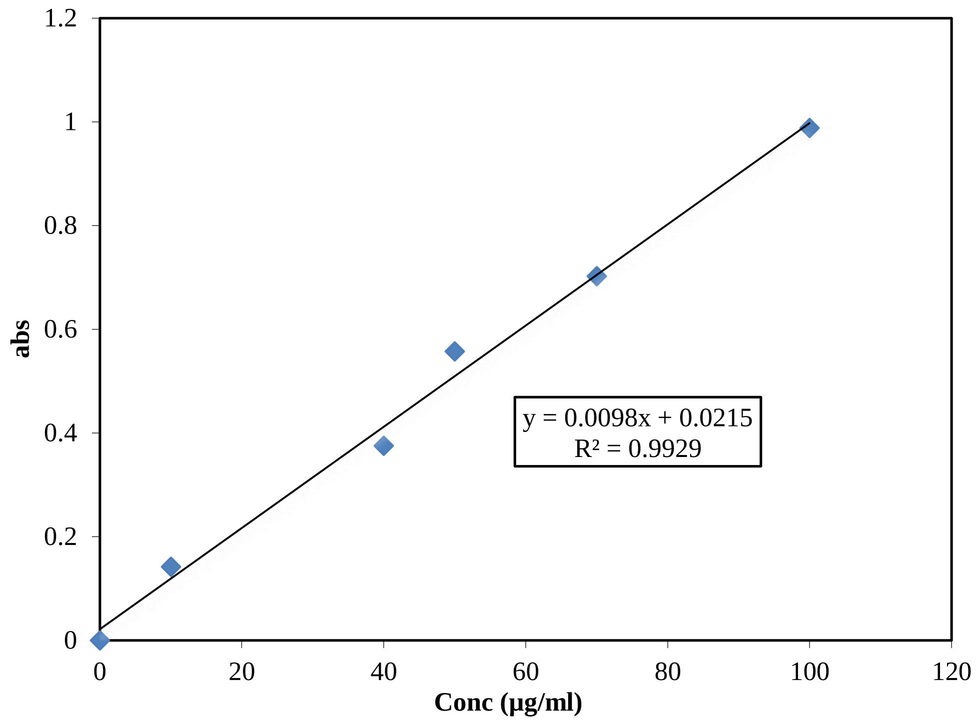

Figure (2): Standard calibration curve of Gallic acid

However, quantitative phenol contents of *S. multicaulis* leave aqueous fraction presented in Table 2 and demonstrated that this fraction contains 14.64±1.53 GAE/g of dry fraction.

Table (2): Quantitative total phenols, and tannins contents of *S. multicaulis* leave hexane, acetone, methanol, and aqueous fractions.

Plant fractions	Total Tannin contents, mg of CAE/g of dry fraction, ±SD	Total phenol contents, mg of GAE/g of dry fraction, ±SD
Hexane	3.95±0.59	-
Acetone	1.54±0.61	-
Methanol	3.95±0.59	-
Aqueous	9.25±2.25	14.64±1.53

Antioxidant activity

As observed in Table 3, the results revealed that *S. multicaulis* four solvents fractions have free radical scavenging property in dose-dependent manner (Fig. 3) and all the screened fractions have potent antioxidant activity as presented in Table 3.

Table (3): The IC_{50} values and DPPH inhibitory activity by *S. multicaulis* four solvents fractions and Trolox.

Conc.	Trolox ±SD	Hexane fraction ±SD	Acetone fraction ±SD	Methanol fraction ±SD	Aqueous fraction ±SD
0	0±0	0±0	0±0	0±0	0±0
2	53.89±3.6	55.47±0.53	59.99±0.53	36.98±0.53	23.21±0.44
5	94.15±0.80	55.47±0.53	61.13±0.53	42.07±0.8	39.84±1.86
10	96.75±1.80	57.35±0.53	65.84±0.26	56.98±1.06	49.4±0.41
20	97.4±1.80	61.5±0.53	73.2±0.01	83.39±0.53	49.4±0.41
50	97.72±2.20	96.79±0.26	76.98±0.53	92.26±0.26	91.69±1.06
100	99.35±0.00	97.73±0.34	82.45±0.80	93.95±0.53	92.45±0.29
IC_{50} (µg/ml) ±SD	2.23±1.57	5.37±0.40	4.78±0.44	6.60±0.62	10.23±0.7

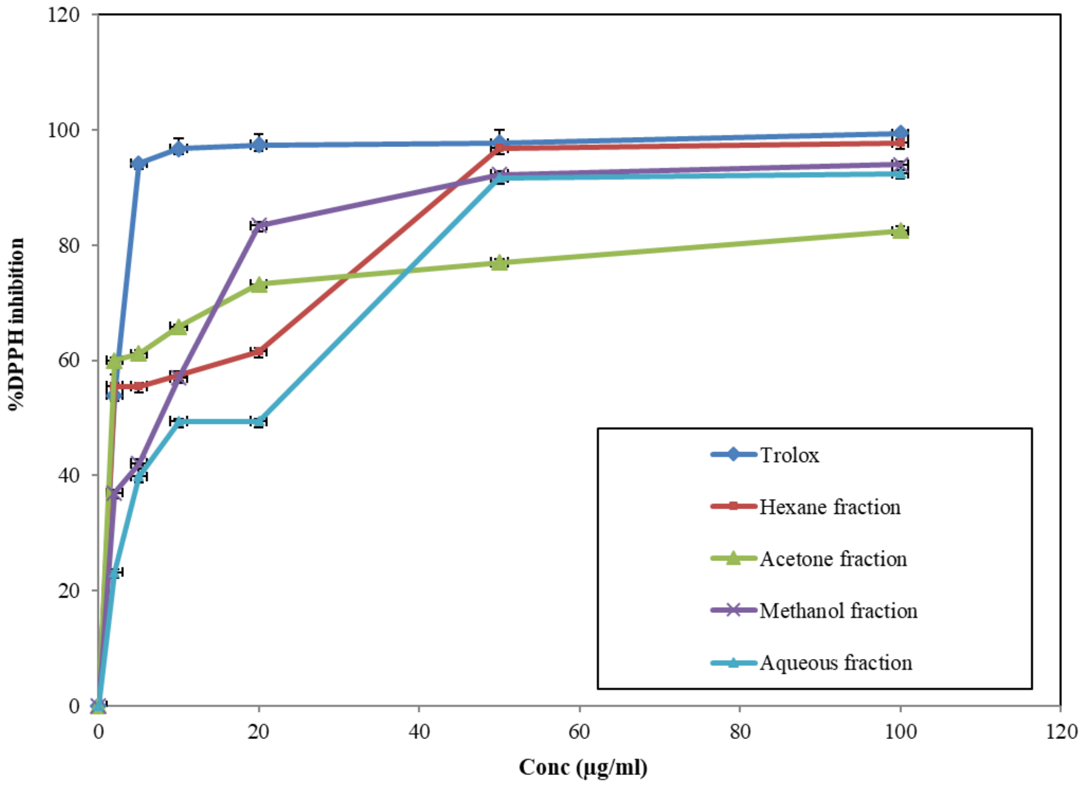

Figure (3): DPPH scavenging properties by *S. multicaulis* four solvents fractions and Trolox.

The antioxidant outcomes revealed that *S. multicaulis* hexane, methanol, acetone and aqueous solvents fractions have potential antioxidant activity while the acetone fraction has the highest antioxidant potential with IC_{50} value of 4.78±0.44 µg/ml in comparison with Trolox a potential free radical scavenging compound and vitamin E analogue which has antioxidant IC_{50} value of 2.23±1.57 µg/ml.

α-Amylase inhibitory activity

Figure 4 depicted the α-amylase inhibitory activity of *S. multicaulis* four fractions in comparison with Acarbose, which is used therapeutically in the management of type 3 of diabetes. Moreover, Table 4 shows the inhibition percentages and the IC_{50} values of all the studied samples. However, the aqueous fraction showed the highest α-amylase inhibitory activity with an IC_{50} value of 158.48±0.62 µg/ml.

Table (4): The α-amylase inhibitory activity by Acarbose drug and *S. multicaulis* four solvents fractions in addition to their IC_{50}values.

Conc.	Acarbose ±SD	Hexane fraction ±SD	Acetone fraction ±SD	Methanol fraction ±SD	Aqueous fraction ±SD
0	0±0	0±0	0±0	0±0	0±0
10	53.22±1.20	8.3±0.24	3.89±0.72	18.47±0.24	38.13±1.20
50	54.91±0.58	10.84±0.96	23.04±0.95	23.38±0.47	38.81±0.24
70	66.1±1.34	24.74±0.96	25.25±0.24	37.28±1.43	61.35±0.96
100	66.1±1.62	24.74±0.96	29.82±0.95	43.04±0.47	63.55±0.24
500	72.54±1.37	26.43±0.95	60.67±1.43	51.69±1.20	65.76±0.48
IC_{50} (µg/ml) ±SD	28.84±1.22	50118±0.81	501.2±0.86	398.1±0.76	158.48±0.62

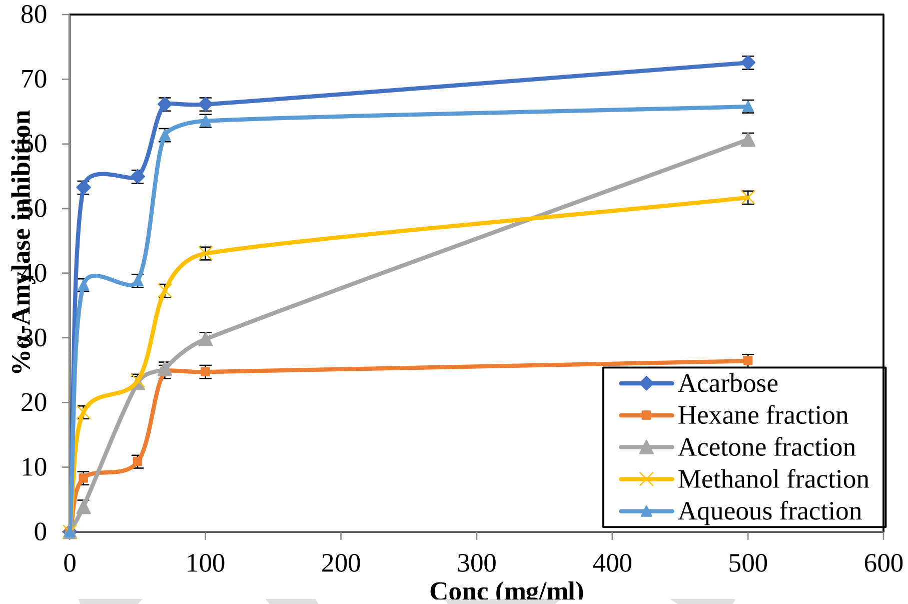

Figure (4): α-Amylase inhibitory activity of *S. multicaulis* four solvents fractions and Acarbose drug.

α-Glucosidase inhibitory activity

Alongside the reference medication Acarbose, α-glucosidase inhibitory activity was investigated for *S. multicaulis* four solvent fractions. When compared to the positive control, Acarbose, which has an IC_{50} value of 37.15±0.33 µg/ml, the findings indicated that the methanolic fraction had the strongest α-glucosidase inhibitory activity (Fig. 5 and Table 5).

Table (5) The α-glucosidase suppressant action by Acarbose drug and *S. multicaulis* four solvents fractions in addition to their IC_{50} doses.

Conc.	Acarbose ±SD	Hexane fraction ±SD	Acetone fraction ±SD	Methanol fraction ±SD	Aqueous fraction ±SD
0	0±0	0±0	0±0	0±0	0±0
100	65.8±0.42	17.49±0.20	25.73±1.03	65.29±0.41	23.21±0.44
200	67.75±0.35	20.29±0.41	32.2±0.21	66.02±1.44	39.84±1.86
300	73.20±0.42	22.2±0.62	35.87±0.41	70.43±0.20	49.4±0.41
400	85.35±0.35	37.64±0.41	66.02±1.03	72.35±0.83	49.4±0.41
500	92.22±0.11	38.96±0.62	66.02±1.03	89.11±0.82	65.44±0.62
IC_{50} (µg/ml) ±SD	37.15±0.33	12589±0.45	389±0.74	39.81±0.74	316.22±0.75

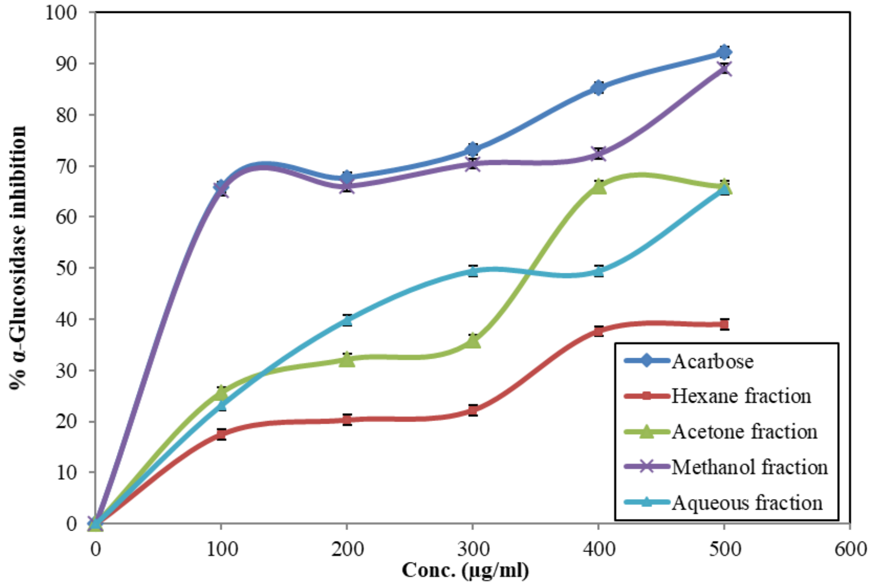

Figure (5): α-Glucosidase inhibitory potentials by Acarbose drug and *S. multicaulis* four solvents fractions.

Antilipase activity

We used the pig pancreatic lipase inhibitory test to assess the antilipase activity of the four fractions of the *S. multicaulis* plant. We compared the results to those of the commercial medication Orlistat, which is a positive control. Table 6 and Fig. 6 demonstrated that, compared to the positive control Orlistat, which had an IC_{50} value of 12.3 ±0.33 µg/ml, the hexane fraction exhibited the strongest antilipase activity at 316.2±0.87 µg/ml.

Table (6): The lipase inhibitory activity by Orlistat drug and *S. multicaulis* four solvents fractions in addition to their IC_{50} values.

Conc.	Orlistat ±SD	Hexane fraction ±SD	Acetone fraction ±SD	Methanol fraction ±SD	Aqueous fraction ±SD
0	0±0±	0±0	0±0	0±0	0±0
50	51.65±0.21	22.49±1.52	11.54±0.5	26.9±0.67	13.68±0.5
100	64.80±0.42	30.59±0.5	11.54±0.5	26.9±0.67	13.68±0.5
200	78.13±0.19	35.59±0.16	20.23±8.41	42.25±0.84	20.94±0.67
300	85.72±0.53	51.3±1.52	40.23±0.16	42.25±0.84	32.49±0.5
400	94.67±0.31	72.13±0.67	42.73±0.16	52.14±0.33	48.8±1.68
IC_{50} (µg/ml) ±SD	12.3 ±0.33	316.2±0.87	6309±1.95	630.9±0.67	645.6±0.77

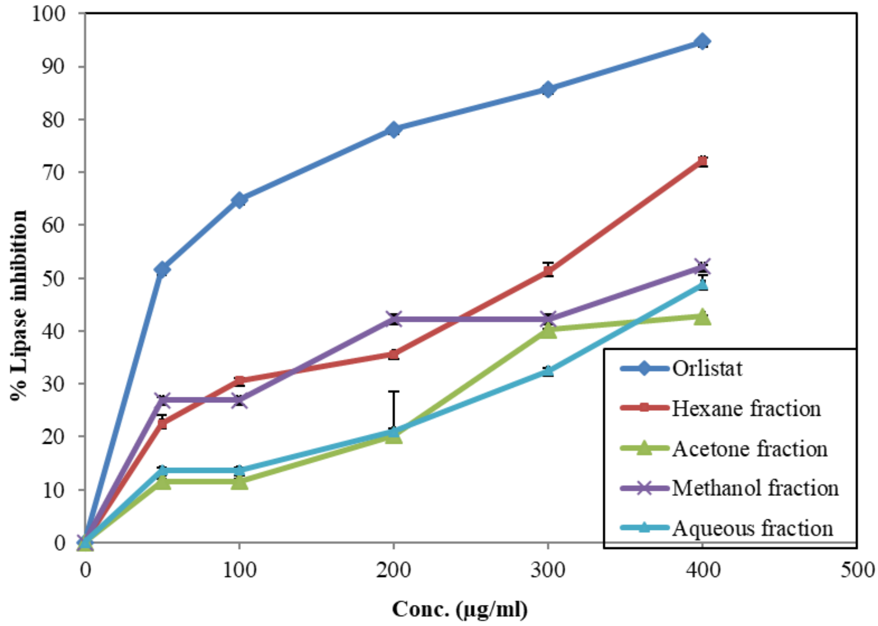

Figure (6): Lipase inhibitory property by Orlistat drug and *S. multicaulis* four solvents fractions.

To the best of the author's knowledge, no previous investigations evaluated the α-amylase, lipase, and α-glycosidase inhibitory activities and the current study will be the first one conducted these experiments.

Discussion

Medicinal plants and phytogenic compounds have been used in traditional medicine worldwide for the treatment of many ailments since ancient times. Crude plant extracts are now recognized as a significant reservoir of natural compounds that may be used in the creation of medications to combat a range of ailments, the formulation of pharmaceutical goods, and innovative biomedical research.

Stiefia multicaulis (synonym *Salvia multicaulis* Vahl) is one of the traditional medicinal plants in Palestine and other Mediterranean regions [24].

Antioxidants are essential in defending against oxidative stress and the harm caused by free radicals, which are triggered by diabetes, cardiovascular diseases, and cancer. The DPPH free radicals screening showed that all *S. multicaulis* hexane, acetone,methanol, and aqueous fractions have potent antioxidant effects compared with Trolox with IC_{50} doses of 5.37±0.40, 4.78±0.44, 6.60±0.62, 10.23±0.7, and 2.23±1.57 µg/ml, respectively. These outcomes agree with a study conducted by Tepe *et al*., which showed that the essential oil and the methanolic extract of *S. multicaulis* have antioxidant activities with IC_{50} values of 2.4±0.05 and 16.3±0.1 µg/ml, respectively [23]. Besides, these results agree with Pehlivan and Sevindik investigation, which found that the *S. multicaulis* ethanolic extract had a potent antioxidant effect [25] .

However, our phytochemical screenings showed that the *S. multicauli* enriches phytochemicals; all extracts also have tannins, and the aqueous extract contains a high amount of phenols. These components, including tannins and phenols, have high potential antioxidant effects [26].

Moreover, the aqueous *S. multicaulis* fraction showed the highest α-amylase inhibitory activity with an IC_{50} value of 158.48±0.62 µg/ml. This outcome may be due to the richness of *S. multicaulis* aqueous fraction with tannins and phenols (9.25±2.25 mg of CAE/g of dry fraction and 14.64±1.53 mg of GAE/g of dry fraction, respectively.

In fact, tannins and phenols are among the most potent antiamyalse agents [27]. Compared to the positive control, Acarbose, which has an IC_{50} value of 37.15±0.33 µg/ml, the findings indicated that the methanolic fraction had the strongest α-glucosidase inhibitory activity (IC_{50}=39.81±0.74 µg/ml). These findings agree with the study by Tamimi et al., which found that plants rich in phytochemicals had potential antiglucosidase effects [28].

S. multicaulis hexane, acetone, methanol, and aqueous fractions revealed mild lipase inhibitory properties compared with Orlistat drug and the hexane fraction showed the highest antilipase effect with IC_{50} dose of 316.2±0.87 µg/ml while Orlistat has antilipase effect IC_{50} dose of 12.3 ±0.33 µg/ml.

Tannins and phenolic molecules, which are found in many crops, have substantial inhibitory effects on digestive enzymes such as lipase, α-glucosidase, and α-amylase. The bioactive substances can attach to these enzymes, which leads to a decrease in their activity and, therefore, reduces the absorption of fats and carbs. This inhibitory process is essential for controlling metabolic diseases such as obesity and diabetes by reducing fat absorption and regulating blood glucose levels after a meal. The mentioned components are derived from green tea, grapes, pomegranates, and nuts and seeds. Their ability to act as both enzyme inhibitors and antioxidants further amplifies their potential health advantages. Therefore, including tannins and phenols in one's diet may provide a natural approach to enhancing metabolic health and controlling chronic illnesses [29].

In fact, to the best of our knowledge, no previous investigations screened the antilipase, antiglucosidase and antiamylase effects of *S. multicaulis* four fractions.

Limitations

The obtained data were done in vitro from crude extract, future studies willl undertaken to study the effects of this plant in vivo from pure compounds.

Conclusion

The obtained data about the *S. multicaulis* aqueous, hexane, methanol, and acetone solvents fractions showed that they have potential antioxidant potentials compared with Trolox. In addition, it can be considered as the first information on the α-amylase, lipase and α-glycosidase inhibitory activities of *S. multicaulis* four solvent fractions. Further investigations are needed to assess the in vivo potential of these plant fractions in animal models.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and materials

This published article and its supplementary information files include all data generated or analyzed during this study.

Author's contribution

BR: Conceptualization, Validation, Investigation, writing – original draft, Writing - review & editing, Visualization, analysis, Supervision, Project administration.

Funding

None

Conflicts of interest

The authors declare that they have no competing interests.

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